Review of Ongoing Clinical Trials in Non-small Cell Lung Cancer

A Status Report for 2009 from the ClinicalTrials.gov Website

Janakiraman Subramanian, MD, Anusha R. Madadi, MD,† Monica Dandona, MD,‡ Kristina Williams,* Daniel Morgensztern, MD,*§ and Ramaswamy Govindan, MD*§*

Introduction: Several new agents are being tested in clinical trials for patients with non-small cell lung cancer (NSCLC). A survey of ongoing clinical trials in NSCLC in the ClinicalTrials.gov website would help identify areas that require further attention in the future.
Methods: We conducted a survey of ongoing clinical trials on NSCLC registered in the ClinicalTrials.gov website. The advanced search option was applied using the terms "non small cell lung cancer," "open studies," "interventional," and "adults 18 years or older."
Results: Of the 493 eligible trials, 77 (15.6%) were phase III, 92 (18.7%) were phase I, and 240 (48.7%) were phase II trials. Universities were listed as the primary sponsor for 224 (45.4%) trials and pharmaceutical industry for 166 (33.7%) trials. Majority of the trials were multicenter studies (56.8%) and were being conducted exclusively within the United States (51.3%). A large proportion of phase II and III clinical trials (77.2%) were focused on patients with advanced-stage disease. The most frequently used end points were progression-free survival (27.1%) followed by tumor response rate (22.9%) and overall survival (16.6%). Although biomarker analysis was included in 185 (37.5%) trials, only 39 (7.9%) trials used biomarkers for patient selection.
Conclusions: Progression-free survival is the end point most commonly used to assess the effectiveness of experimental regimens, and biomarker-based patient selection is rarely used in ongoing clinical trials for NSCLC.

(*J Thorac Oncol.* 2010;5: 1116–1119)

Lung cancer is the leading cause of cancer-related death in the United States. In 2009, it was estimated that there would be 219,440 new cases and 159,000 deaths from lung cancer in the United States.[1] The fact that lung cancer clinical trials account for 14% of ongoing oncology trials worldwide is a testament to the vigorous interest in pursuing novel treatment options for this disease.[2]

Successful introduction of a new anticancer drug in the United States requires regulatory approval by the Food and Drug Administration. It takes more than 9 years to complete the required preclinical studies and a series of clinical trials.[3] Drug development is an expensive process,[4] more specifically, the clinical trials are very expensive. Vast majority of cancer clinical trials fail to reach their stated end points.[3]

With the availability of several new agents, numbers of clinical trials have increased exponentially. For the first time in the history of clinical research, we could now survey currently ongoing clinical trials using a publicly available database to obtain useful information not only on the current trends in cancer research but also learn how to prioritize future research. More importantly, a periodic review (annually or biannually) of the process will be necessary to provide the necessary perspective and framework for drug development in the future. The ClinicalTrials.gov website is a registry for clinical trials and provides valuable information on ongoing clinical trials. This registry was established by the Department of Health and Human Services through the National Institutes of Health with the primary purpose of improving public access to clinical trials, and it currently contains approximately 85,760 clinical trials. Furthermore, the International Committee of Medical Journal Editors (ICMJE) requires that all clinical trials be enrolled in a public registry before patient enrollment if they are to be considered for publication. The ClinicalTrials.gov website states that it "provides a vehicle which allows organizations and individuals to provide the data requested by ICMJE" (http://prsinfo.clinicaltrials.gov/icmje.html). We conducted a survey of ongoing clinical trials listed in the ClinicalTrials.gov website for patients with non-small cell lung cancer (NSCLC).

PATIENTS AND METHODS

We used the advanced search option available on the ClinicalTrials.gov website using the search term "non small cell lung cancer." In the drop down menus, we chose "open studies" for recruitment status and "interventional" for study type. We excluded age group "birth to 17 years of age" in additional criteria. Our study included all trials reported until June 2, 2009, in the website. We excluded trials that did not

*Division of Oncology, Department of Medicine, Washington University School of Medicine; †Department of Medicine, St. Luke's Hospital; ‡Department of Medicine, Washington University School of Medicine; and §Alvin J. Siteman Cancer Center at Washington University School of Medicine, St. Louis, Missouri.
Disclosure: The authors declare no conflicts of interest.
Address for correspondence: Ramaswamy Govindan, MD, Division of Medical Oncology, Washington University School of Medicine, 660 S. Euclid, Box 8056, St Louis, MO 63110. E-mail: rgovinda@dom.wustl.edu

ISSN: 1556-0864/10/0508-1116

involve patients with NSCLC and clinical trials that did not include any form of medical therapy.

We extracted the following information: (1) type of clinical trial (phase I, II, or III), (2) recruiting status, (3) tumor, node, metastasis stage, (4) study design: randomization, control group, and number of study arms, (5) location, (6) the number of trial centers, (7) primary sponsor, (8) target enrollment, (9) treatment setting, (10) treatment modality, (11) date of trial activation, (12) time elapsed since the study was open for enrollment, and (13) primary outcome measure.

RESULTS

Our search identified 658 trials of which 165 were excluded, because they involved patients with small cell lung cancer or did not include any form of medical therapy in the study arm. Of the 493 trials selected, 472 (95.7%) were actively recruiting and 19 (3.9%) were not yet open for enrollment. However, two (0.4%) trials were listed as closed to enrollment despite choosing the option "open" in the drop down menu for recruitment status in the advanced search option. Based on an intention to treat principle, we included these two trials in our analysis. Majority of the studies were phase II trials (240, 48.7%) followed by phase I (92, 18.7%), phase III (77, 15.6%), and phase I/II trials (61, 12.4%). Two hundred twenty-four clinical trials (45.4%) were sponsored by universities, 166 (33.7%) by pharmaceutical industry, and 43 (8.7%) by cooperative groups. Nearly half of the studies were conducted exclusively within the United States (51.3%) and in multiple locations (56.8%) (Table 1).

TABLE 1. Characteristics of All Open Clinical Trials in ClinicalTrials.gov

	Number of Trials (%)
Type of clinical trials	
Phase I	92 (18.7)
Phase II	240 (48.7)
Phase I/II	61 (12.4)
Phase III	77 (15.6)
Phase II/III	3 (0.6)
Phase IV	8 (1.6)
Unspecified	12 (2.4)
Primary sponsor	
Industry	166 (33.7)
Cooperative group	43 (8.7)
University	224 (45.4)
NCI	18 (3.7)
Others	42 (8.5)
Recruiting status of clinical trials	
Actively recruiting	472 (95.7)
Not yet open for recruitment	19 (3.9)
Closed to recruitment but still open	2 (0.4)
Number of study locations	
Single study location	213 (43.2)
Multiple study locations	280 (56.8)
Location of trial centers	
In United States	253 (51.3)
Outside United States	177 (35.9)
Both	63 (12.8)

NCI, National Cancer Institute.

TABLE 2. Characteristics of Phase II and III Clinical Trials

Study Design	Number of Phase II Trials (%)[a]	Number of Phase II/III Trials (%)	Number of Phase III Trials (%)
Randomization			
Randomized trials	108 (35.9)	3 (100)	77 (100)
Nonrandomized trials	193 (64.1)		
Open label	265 (88.0)	2 (66.7)	45 (58.4)
Single blinded	1 (0.3)		1 (1.3)
Double blinded	25 (8.3)	1 (33.3)	24 (31.2)
Unknown	10 (3.3)		7 (9.1)
Number of treatment arms			
Single arm	183 (60.8)		
Two arms	97 (32.2)	3 (100)	69 (89.6)
Three or more arms	21 (7.0)		8 (10.4)
Type of control arm			
Placebo	5 (1.7)	2 (66.7)	13 (16.9)
Standard care or active control	102 (33.9)	1 (33.3)	64 (83.1)
Uncontrolled	194 (64.4)		
Primary outcome			
Overall survival	32 (10.6)		50 (64.9)
Progression-free survival	106 (35.2)	3 (100)	21 (27.3)
Tumor response rate	111 (36.9)		1 (1.3)
Quality of life	3 (1.0)		1 (1.3)
Efficacy/feasibility	10 (3.3)		1 (1.3)
Others or unspecified	38 (12.7)		2 (2.6)
Disease-free survival	1 (0.33)		1 (1.3)

[a] Includes phase I/II studies and phase II studies.

A significant proportion of the phase II trials (including the phase II portion of phase I/II trials) were nonrandomized (64.1%), open-label (88%), or had single-arm (60.8%). In phase III trials, the experimental regimen was compared with standard of care or active control in 64 (83.1%) trials and best supportive care only in 13 (16.9%) trials (Table 2). In addition, 45 (58.4%) phase III trials had an open-label design. The median number of patients planned for enrollment was 65.5 (range, 3–600) in phase II trials and 600 (range, 80–2270) in phase III trials. Progression-free survival was the primary outcome in 27.1% of all trials followed by tumor response rate in 22.9% and overall survival in 16.6%. Other primary outcomes measured were quality of life, disease-free survival, immunologic responses, or traditional phase I end points. Response rate was the primary end point in 36.9% of phase II trials, followed by progression-free survival in 35.2% and overall survival in 10.6%. Other primary outcomes measured in phase II trials were safety and toxicity, immunologic response, quality of life, and disease-free survival. Overall survival was the primary outcome measure in nearly two-thirds of all phase III studies, whereas progression-free survival was the primary end point in the remaining one-third.

A large proportion (77.2%) of the phase II and III clinical trials were focused on patients with advanced-stage disease, with 34.1% of the trials on first-line chemotherapy, 34.7% on second-line or more, and 2.9% on maintenance therapy (Table 3). Only 10% of the clinical trials involved concurrent chemotherapy and radiation. The proportion of

TABLE 3. Treatment Setting in Phase II and III Clinical Trials

Treatment Setting[a]	Number of Trials (%)
Chemoprevention trials	2 (0.5)
Adjuvant therapy	22 (5.8)
Neoadjuvant therapy	18 (4.7)
Adjuvant/neoadjuvant therapy	7 (1.8)
Concurrent chemoradiotherapy	38 (10.0)
Advanced-stage disease	
First line	130 (34.1)
First or second line	7 (1.8)
Second line or more	132 (34.7)
Maintenance	11 (2.9)
Unspecified	14 (3.7)

[a] Includes phase I/II, II, II/III, and III trials.

TABLE 4. Clinical Trials on Targeted Agents in the Treatment of NSCLC

		Combination		
Targeted Agents[a]	Single Agent	With Targeted Agents	With Chemotherapy	With Other Agents
EGFR inhibitors	47 (39.8)	31 (26.3)	34 (28.8)	5 (5.1)
VEGF inhibitors	17 (18.5)	12 (13.0)	62 (67.4)	1 (1.1)
mTOR inhibitors	2 (33.3)	1 (16.7)	3 (50.0)	—
Histone deacetylase inhibitors	1 (12.5)	4 (50.0)	3 (37.5)	—
IGF receptor antagonists	—	5 (45.4)	6 (54.6)	—
HER2 receptor antagonists	5 (71.4)	1 (14.3)	1 (14.3)	—
Proapoptotic agents	—	1 (33.3)	2 (66.7)	—
Proteasome inhibitors	2 (33.3)	1 (16.7)	3 (50.0)	—
Others	11 (31.4)	8 (22.9)	15 (42.8)	1 (2.9)

[a] Includes phase I/II, II, II/III, and III trials.

EGFR, epidermal growth factor receptor; VEGFR, vascular epidermal growth factor receptor; mTOR, mammalian target of rapamycin; IGF, insulin growth factor; NSCLC, non-small cell lung cancer.

TABLE 5. Clinical Trials with Biomarker Analysis

Characteristics	*n* (%)
Biomarker(s) specified	185
Yes	145 (78.4)
No	40 (21.6)
Phase of the trial	
Phase I	34 (18.4)
Phase I/II	20 (10.8)
Phase II	93 (50.3)
Phase II/III	1 (0.5)
Phase III	27 (14.6)
Phase IV	1 (0.5)
Not specified	9 (4.9)
Treatment regimen	
Targeted therapy	79 (42.7)
Combined chemotherapy with targeted agents	46 (24.9)
Chemotherapy trials only	24 (13.0)
Immune	23 (12.4)
Alternative	2 (1.1)
Others	11 (5.9)

TABLE 6. Time Line for Patient Enrollment in Phase II Trials

	0–12 mo	>12–24 mo	>24 mo
All phase II trials	93 (38.8)	56 (23.3)	91 (37.9)
Industry sponsor	41 (62.1)	14 (21.2)	11 (16.7)
Cooperative group	10 (38.5)	10 (38.5)	6 (23)
University sponsor	31 (25.4)	27 (22.1)	64 (52.5)
Other sponsors	7 (33.3)	5 (23.8)	9 (42.9)
NCI sponsor	4 (80)	-	1 (20)

NCI, National Cancer Institute.

trials for patients with early-stage NSCLC receiving adjuvant or neoadjuvant therapy was 12.3%.

Cytotoxic chemotherapy was the primary treatment modality in 26.8% of all phase II and phase III clinical trials; targeted agents in 29.1%; combined cytotoxic and targeted therapy in 30.1%; and others including immunomodulators, chemosensitizing agents, and alternate therapies in 14%.The commonly studied targeted agents in these trials were epidermal growth factor receptor (EGFR) inhibitors and vascular epidermal growth factor receptor tyrosine kinase inhibitors. Other targeted agents included histone deacetylase inhibitors, insulin growth factor inhibitors, proteasome inhibitors, and proapoptotic agents (Table 4). EGFR inhibitors were more likely to be evaluated as single agents (39.8%) than vascular epidermal growth factor receptor inhibitors (18.5%).

Biomarker analysis was included as one of the study objectives in 185 (37.5%) of the total 493 trials. Of the 185 trials, 34 (18.4%) were phase I trials, 20 (10.8%) were phase I/II trials, 93 (50.3%) were phase II trials, and 27 (14.6%) were phase III trials (Table 5). Of the trials that included biomarker analysis, monotherapy with a targeted agent was studied in 79 (42.7%) trials, combined chemotherapy and targeted therapy in 46 (24.9%) trials, and chemotherapy alone in 24 (13.0%) trials. More importantly, biomarker-based patient selection was used in only 39 trials (7.9%). EGFR expression or mutation status was the most common biomarker in 17 (43.6%) trials used to select patients followed by K-ras mutation status in five (12.8%) trials and markers for DNA repair in five trials (12.8%).

Because the time line for patient enrollment is quite different for phase II and phase III studies, we analyzed them separately. A significant proportion of phase II trials with universities listed as primary sponsor were open for more than 2 years (52.5%) compared with trials sponsored by co-operative group (23%) or industry (16.7%) (Table 6). A similar trend was observed in phase III trials as well, with 50% of all university-sponsored trials open for more than 3 years compared with 23.0% of cooperative group and 18.2% of industry-sponsored trials (Table 7).

DISCUSSION

Our survey of the ClinicalTrials.gov web site suggest that more than half of all ongoing clinical trials in NSCLC are phase II trials. Majority of the clinical trials for NSCLC are conducted in multiple centers across the United States and

TABLE 7. Time Line for Patient Enrollment in Phase III Trials

	0–12 mo	>12–24 mo	>24–36 mo	>36 mo
All phase III trials	21 (27.2)	22 (28.6)	11 (14.3)	23 (29.9)
Industry sponsor	13 (39.4)	9 (27.3)	5 (15.1)	6 (18.2)
Cooperative group	4 (30.8)	4 (30.8)	2 (15.4)	3 (23.0)
University sponsor	3 (16.7)	5 (27.8)	1 (5.5)	9 (50.0)
Other sponsors	—	4 (36.4)	2 (18.1)	5 (45.5)
NCI sponsor	1 (50)	—	1 (50)	—

NCI, National Cancer Institute.

sponsored by the universities. It is worth noting that not all clinical trials conducted outside the United States are listed in the ClinicalTrials.gov website. In fact, there are several international registries that meet the ICMJE criteria for public clinical trial registries. The World Health Organization website provides a list of these international clinical trial registries (http://www.who.int/ictrp/network/primary/en/index.html). Both phase II and phase III clinical trials sponsored by universities were open for a longer period of time than trials sponsored by industry or co-operative group.

A number of high-profile phase III studies in NSCLC published recently have failed to reach their primary end points. Novel phase II designs have been developed to enhance the likelihood of success for the experimental regimen in the phase III setting.[5–14] Even though it has been shown to be a suboptimal end point, response rate continues to be used as a primary end point in majority of phase II trials.[5,7,12] Quite disappointingly, the majority of phase II studies we analyzed for this report were staid and formulaic. In general, these single-arm phase II studies were not designed to develop biomarkers that could then be tested further in large clinical studies. In the absence of serious and thoughtful effort to develop biomarkers in phase I or phase II trials, it is not surprising that most of the phase III studies in NSCLC conducted with molecularly targeted agents today are not biomarker driven.

It is unlikely that the current approach of using molecularly targeted agents with a narrow spectrum of activity would benefit an unselected population of patients with a disease as diverse as NSCLC. Clearly, a thorough understanding of the drug, the target pathway(s), and potential factors that could modulate pathways of interest is essential before launching large-scale clinical trials. Insights gained from the clinical studies should truly promote a dynamic and constant two-way interaction between the bench and clinic. Tissue collection should be mandatory even in advanced disease settings, and a systematic attempt should be made to identify predictive biomarkers in phase II studies.

It is disappointing to note that the number of clinical trials for early-stage and locally advanced NSCLC is disproportionately low compared to advanced stage disease. Most patients with advanced-stage disease do not have adequate tumor tissue available for biomarker development and when available, archived tumor tissue samples stored at the time of diagnosis may not be relevant in patients with relapsed/refractory disease.

A significant proportion of patients with early-stage NSCLC relapse despite undergoing curative surgery or even postoperative systemic therapy.[15–17] Diligent use of molecularly targeted agents in a well-defined cohort of patients selected based on the biomarker status could dramatically improve the cure rates in early-stage NSCLC. Moreover, the preoperative setting may provide a window of opportunity to evaluate novel targeted agents and develop predictive biomarkers. The current tendency to develop phase III studies based on questionable or marginally "positive" data should be discouraged. It is not just the cumulative burden of repeated failures driving up the cost of drug development process that eventually ricochets through a creaky health system with high drug prices, but the disturbing possibility that an agent quite effective in a small molecularly defined population may never be developed after a negative study in a broad undefined population. The current model may have served us well in the bygone era dominated only by cytotoxic chemotherapies. Clinical trial processes for cancer therapy in general and NSCLC in particular should be adapted and retailored to evaluate these novel agents, celebrated for their narrow spectrum of targets, systematically and thoughtfully. As with many things in life, a constant re-evaluation of the current status and remodeling of our approach is necessary if we want to make significant progress.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. *CA Cancer J Clin* 2009;59:225–249.
2. Seruga B, Hertz PC, Le LW, et al. Global drug development in cancer: a cross-sectional study of clinical trial registries. *Ann Oncol* 2009;21:895–900.
3. DiMasi JA, Grabowski HG. Economics of new oncology drug development. *J Clin Oncol* 2007;25:209–216.
4. Adams CP, Brantner VV. Estimating the cost of new drug development: is it really 802 million dollars? *Health Aff (Millwood)* 2006;25:420–428.
5. Chen TT, Chute JP, Feigal E, et al. A model to select chemotherapy regimens for phase III trials for extensive-stage small-cell lung cancer. *J Natl Cancer Inst* 2000;92:1601–1607.
6. Freidlin B, Breathnach OS, Johnson BE. A model to select regimens for phase III trials for patients with advanced-stage non-small cell lung cancer. *Clin Cancer Res* 2003;9:917–922.
7. Chan JK, Ueda SM, Sugiyama VE, et al. Analysis of phase II studies on targeted agents and subsequent phase III trials: what are the predictors for success? *J Clin Oncol* 2008;26:1511–1518.
8. Goffin JR, Tu D. Phase II stopping rules that employ response rates and early progression. *J Clin Oncol* 2008;26:3715–3720.
9. Inoue LY, Thall PF, Berry DA. Seamlessly expanding a randomized phase II trial to phase III. *Biometrics* 2002;58:823–831.
10. Schiller JH. Clinical trial design issues in the era of targeted therapies. *Clin Cancer Res* 2004;10:4281S–4282S.
11. Wieand S, Schroeder G, O'Fallon JR. Stopping when the experimental regimen does not appear to help. *Stat Med* 1994;13:1453–1458.
12. Zia MI, Siu LL, Pond GR, et al. Comparison of outcomes of phase II studies and subsequent randomized control studies using identical chemotherapeutic regimens. *J Clin Oncol* 2005;23:6982–6991.
13. Herndon JE II. A design alternative for two-stage, phase II, multicenter cancer clinical trials. *Control Clin Trials* 1998;19:440–450.
14. Parmar MKB, Barthel FM-S, Sydes M, et al. Speeding up the evaluation of new agents in cancer. *J Natl Cancer Inst* 2008;100:1204–1214.
15. Ravdin PM, Davis G. Prognosis of patients with resected non-small cell lung cancer: impact of clinical and pathologic variables. *Lung Cancer* 2006;52:207–212.
16. Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest* 1997;111:1710–1717.
17. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. *J Thorac Oncol* 2007;2:706–714.

